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Review article

Beneficial immune activity after CNS injury: prospects for vaccination

Michal Schwartz*, Gila Moalem

Department of Neuroimmunology, The Weizmann Institute of Science, Rehovot, Israel

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Abstract

A recent study in our laboratory showed, against all expectations, that macrophages and a particular type of T cell, by promoting regrowth and reducing the post-traumatic spread of damage in the injured rat optic nerve or spinal cord, have a beneficial effect on the injured CNS. Macrophages in the CNS have long been thought to have predominantly destructive effects. Autoimmunity in general, and in the CNS in particular, has never been documented as a purposeful physiological response of benign character. Our results suggest that after traumatic injury to the central nervous system (CNS), both of these immune cell types potentially have beneficial effects: macrophages can promote repair and T cells of a particular specificity can reduce the spread of damage. However, possibly because of the immune-privileged character of the CNS, the spontaneously evoked physiological activities of both macrophages and T cells in the CNS are restricted, and appear to need well-controlled boosting in order to be effective. It thus appears that (i) a stress signal transmitted from the traumatized tissue (in this case the CNS) for recruitment of the adaptive immune system does not have to be pathogen-related in order to evoke a response, (ii) a response to self is not necessarily a quirk of nature, and (iii) an autoimmune response, provided that it is well-regulated, helps the individual to cope with stress signals from the traumatized CNS, and thus plays a role in maintenance of the injured tissue without posing a threat to the organism.

Keywords: CNS injury; Macrophages; T cells

1. Dialog between the intact CNS and immune system

The interaction between the central nervous system (CNS) and the immune system is unique, partly because it is characterized by 'immune privilege', involving restriction of local immune responses within the CNS. This phenomenon might be an evolutionary adaptation developed to protect the intricate neuronal networks of the CNS from potentially disruptive incursion by the immune system (Lotan and Schwartz, 1994; Schwartz et al., 1999a; Schwartz, 2000).

What do we mean by CNS immune privilege? An early definition was based on the assumption that the immune system ignores the CNS. This concept of immune ignorance was supported by the observed inability of the CNS to reject allografts, i.e. tissue grafts from the same species but from a different major histocompatibility complex (MHC) haplotype. Immune privilege was thought to be maintained by the harboring of antigens within the CNS and the inability of immune cells to enter the CNS under normal physiological conditions. Any entry of leukocytes was viewed as evidence of pathology (Cserr and Knopf, 1992; Cserr et al., 1992; Griffin et al., 1997; Hickey et al., 1991; Shrikant and Benveniste, 1996).

Several observations have challenged this definition. Firstly, CNS antigens can escape and induce immune responses in the host. Secondly, activated T cells have been found to enter the CNS in the absence of discernible neuropathology. Thirdly, leukocyte recruitment into the CNS appears to successfully resolve some CNS viral infections, such as Sindbis virus encephalitis, without the development of any apparent long-term bystander effects. Fourthly, based on the relatively more prolonged survival of xenografts (tissue grafts from different species) in immunosuppressed individuals, it was proposed that CNS xenograft failures can be attributed, at least in part, to immune system participation. Taken together, these findings indicate that the CNS is accessible to immune cells, and that immune privilege is the result of an active barrier, or of several mechanisms collectively endowing the CNS with unique immune characteristics (Bell et al., 1996; Goverman et al., 1997; Matyszak and Perry, 1995; Matyszak et al., 1997; Perry et al., 1987).

*Corresponding author. Tel.: +972-8-342-467; fax: +972-8-344-131.
E-mail address: michal.schwartz@weizmann.ac.il (M. Schwartz).

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The following mechanisms apparently help to make the CNS a site of immune-privilege.

1. Isolation of the CNS behind the blood–brain barrier, coupled with the absence of draining lymph nodes (Barker and Billingham, 1977) that would prohibit direct communication between the CNS and the immune system. The blood–brain barrier plays an essential role in restricting the entry of cells and molecules into the CNS. It is not, however, the only mechanism restricting their entry (Fabry et al., 1994). Brain regions without a complete blood–brain barrier, such as the circumventricular organs (pineal gland, area postrema, and subfornical organ), are exposed directly to blood plasma constituents, yet do not allow immune cell infiltration or inflammation under normal conditions (Pedersen et al., 1997; Weller et al., 1997; Yamada et al., 1991).
2. Absence of resident antigen-presenting cells. T cell activation requires the delivery of at least two signals: the presence of MHC class II antigens (signal 1) and the presence of costimulatory molecules (signal 2). Lack of one of the signals results in T cell anergy or T cell inactivation. The cells in the CNS that most closely resemble antigen-presenting cells are the microglia. When isolated from normal CNS tissue, microglia constitutively express at least one member of the B7 family (B7.2) required for the delivery of 'signal 2' to T cells, as well as additional costimulatory molecules, such as intracellular adhesion molecule-1 and CD40, which increase and regulate the differentiation of T cell effector phenotypes in the periphery. In the absence of pathology, most microglia do not express detectable levels of MHC class II molecules (signal 1) and hence cannot effectively present antigen to T cells. However, many nonspecific stress signals, including lipopolysaccharides, bacterial antigens, stroke, epileptic seizure activity, and overproduction of cytokines and chemokines, rapidly induce the in-vivo expression of MHC class II molecules, as well as of the costimulatory molecule B7.1 (Kreutzberg, 1996; Perry et al., 1993; Perry, 1998; Shrikant and Benveniste, 1996; Sriram and Rodriguez, 1997). Microglia were found to be poor stimulators of T cell proliferation and interleukin-2 (IL-2) secretion even after the induction of MHC class II molecules (Ford et al., 1996). In astrocytes, MHC class II expression in vivo is undetectable or very low. However, numerous studies have demonstrated that astrocytes can be induced to express MHC class II molecules in vitro, although they are unable to support a primary T-cell proliferative response.
3. CNS-directed deviation and suppression of immune responses. The early responses of microglia to nonspecific stress signals, such as lipopolysaccharides, bacterial antigens and stroke, include the production of molecules such as prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), nitric oxide and others, which have nonspecific cytotoxicity and are deleterious to CNS neuronal function and survival. Nonetheless, despite their potential for neuronal impairment, they may be necessary for the limitation and modulation of immune responses in the CNS. For example, inhibition of NO production increases the susceptibility of otherwise resistant rats to the inflammatory demyelinating disease, experimental autoimmune encephalomyelitis (EAE) (Cowden et al., 1998). PGE2 exerts some protective effects in the CNS: it decreases the expression of costimulatory molecules and MHC on antigen-presenting cells which infiltrate the CNS during acute pathology; it inhibits T cell proliferation directly; and it shifts T cell differentiation toward the more protective T helper cell type 2/3 (Th2/3) phenotype (associated with production of IL-4, IL-10, and transforming growth factor-β (TGF-β)), rather than the Th1 phenotype (associated with interferon-γ (IFN-γ) and TNF-α production) (Hilkens et al., 1995; Lenschow et al., 1996). In response to a variety of inflammatory signals, microglia also produce neuroprotective molecules such as neurotrophins and TGF-β (Elkabes et al., 1996; Heese et al., 1998; Miwa et al., 1997), which can affect CNS inflammation. Cerebrospinal fluid from mice has been shown to contain TGF-β and to force macrophages to present antigens in a deviant manner, thus suppressing T cell activation in the CNS (Wilbanks and Streilein, 1992).

In vitro studies provide evidence that microglia, although unable to present antigens in a context that initiates a proliferative response, can present them in a way that induces either cytokine synthesis by T cells or T cell death. Microglia constitutively express Fas ligand (FasL), a 40-kDa cell-surface protein that binds to its receptor, Fas, and induces apoptosis (Moalem et al., 1999a). They can thus trigger apoptosis in susceptible Fas-expressing cells such as activated T cells, especially during antigen presentation (Bonetti and Raine, 1997; Bonetti et al., 1997; Moalem et al., 1999a). The wide range of proinflammatory and protective factors secreted by astrocytes suggests that these cells play a role in the regulation of CNS immune responses (Merrill and Benveniste, 1996; Shrikant and Benveniste, 1996). Numerous in vitro studies have directly demonstrated the capacity of the astrocytes or of the secreted factors to inactivate T cells and microglia/macrophages (Bauer et al., 1995; Gold et al., 1996; Meinl et al., 1994; Sun et al., 1997; Weber et al., 1994; Xiao et al., 1998). For example, nonactivated astrocytes down-regulate T cell receptor expression and reduce antigen-specific proliferation and cytokine production of myelin basic protein (MBP)-reactive T cells (Sun et al., 1997). Studies in vivo have shown that T cells isolated from the brains of mice with Sindbis virus encephalitis expressed activation markers; however, these T cells were arrested in

the cell cycle and did not proliferate in vitro. While the brain-derived T cells generated IFN-γ, IL-4, and IL-10, these T cells were deficient in IL-2 production relative to peripheral T cells. When T cells producing both IL-2 and IFN-γ were adoptively transferred into Sindbis virus-infected mice, some of these cells entered the brain. Those that did so selectively down-regulated IL-2 production over time, demonstrating that the local environment of the CNS in mice infected with Sindbis virus encephalitis exerts a complex regulatory effect on T cells that are recruited into the brain (Irani et al., 1997).

In view of all the above evidence, it seems that local immune responses within the CNS are regulated by a number of features that result from its unique structure and environment. The CNS probably uses elements of all of these mechanisms for limiting immune responses in an integrated way, with important consequences for normal CNS function. The effects of these mechanisms on the CNS response to injury are summarized below.

2. Dialog between the injured CNS and the immune system

Axonal injury causes degeneration of directly injured fibers, with subsequent death (usually by apoptosis) of their cell bodies. In partial injuries, fibers that escaped the initial insult are eventually also affected, as the damage spreads to neighboring neurons causing secondary degeneration. In the immune-privileged CNS, the recruitment of macrophages and microglia after injury is limited and is mainly confined to the lesion site, unlike the massive recruitment and widespread distribution of macrophages after injury to peripheral nerves (Hirschberg et al., 1994; Lazarov-Spiegler et al., 1996; Perry et al., 1987).

Comparative studies in our laboratory demonstrated that the accumulation of endogenous T cells in the crush-injured rat sciatic nerve (part of the peripheral nervous system (PNS)) was significantly greater than in the crush-injured rat optic nerve (part of the CNS) (Hirschberg et al., 1998). Furthermore, there was extensive death of the T cells that accumulated in the injured optic nerve, but very little T cell death in the injured sciatic nerve (Moalem et al., 1999a). These studies also showed that MHC class II antigens are constitutively expressed in the sciatic nerve but are induced only after injury in the optic nerve, and that expression of FasL protein is more pronounced in the optic than in the sciatic nerve (Moalem et al., 1999a). Thus, the T cell response to CNS injury, represented by the optic nerve, was restricted by the low expression of MHC class II antigens, pronounced FasL expression and the elimination of infiltrating lymphocytes through cell death (Moalem et al., 1999a). Other studies have indicated that FasL might participate in an active mechanism for eliminating invading lymphocytes from immune-privileged sites, including the CNS.

3. Implantation of activated macrophages promotes CNS regrowth

Because the PNS, unlike the CNS, can regenerate after injury, the above results defining the differences between the injury-induced inflammatory responses of the CNS and the PNS have proved helpful in identifying the factors important for nerve recovery. Thus, for example, the observed differences between injured CNS and PNS white matter with respect to macrophage invasion was shown to correlate with differences in the clearance of myelin debris between the two systems (George and Griffin, 1994; Lazarov-Spiegler et al., 1998a,b; Perry et al., 1995; Steeves et al., 1994; Stoll et al., 1989).

These results, together with other findings (David et al., 1990), led us to propose that in the injured CNS, as in other injured tissues, activated macrophages are needed at an early stage after injury in order for healing to take place. This hypothesis was substantiated experimentally in our laboratory by incubating peripheral blood macrophages with PNS or CNS tissue in vitro and then applying equal numbers of macrophages to the site of injury in the optic nerve or spinal cord model. By means of anterograde and retrograde labeling of the transected optic nerves of adult rats, it was demonstrated morphologically that PNS-activated macrophages are more beneficial for axonal regrowth than are CNS-activated or nonactivated macrophages. Regrowth of the CNS axons was correlated with the speedy clearance of myelin from the treated axons and the abundant distribution of PNS-activated macrophages along the distal part of the damaged axons (in contrast to the limited distribution of macrophages in untreated transected axons or in transected axons exposed to CNS-activated macrophages or to nonactivated macrophages). In rats with completely transected spinal cords, partial recovery was manifested by locomotor activity, tested in an open field by measurement of the generation of motor-elicited potential responses in the hindlimb muscles, and by morphological changes that met specific criteria (Lazarov-Spiegler et al., 1998a). It was suggested that the implanted macrophages do no more than convert the extracellular environment of the injured axons into a supportive mode in synchrony with the needs of the regrowing axons. The above data support three conclusions: (1) the CNS is not intrinsically refractory to the processes of healing and regrowth. (2) The ability of activated macrophages to promote CNS healing and regrowth is, in principle, not unlike that promoted by the innate inflammatory response in other organs. (3) The failure of the CNS to regrow can be attributed, at least in part, to a relative inability of the damaged CNS to recruit and activate a timely restorative

inflammatory response to tissue damage (Lazarov-Spiegler et al., 1998b).

4. Autoimmune T cells display a neuroprotective effect

The increased accumulation of T cells observed at the site of a CNS lesion relative to that seen in the healthy CNS (Schluesener and Wekerle, 1985; Hirschberg et al., 1998) raised an intriguing question: are these cells beneficial but too few in number to be effective, or are they harmful and should we therefore remove or modulate them? Studies in our laboratory showed that in injured nerves, systemic administration of T cells of various specificities resulted in a further increase in T cell accumulation at the lesion site, irrespective of the specificity of the injected cells (Hirschberg et al., 1998; Moalem et al., 1999a).

The spread of damage beyond the initial injury (secondary degeneration) after traumatic injury to the CNS has been attributed to biochemical and metabolic changes resulting from the primary cellular damage. These changes include abnormal intracellular shifts of ions such as Na^+ and Ca^{2+}, free radical-associated lipid peroxidation of cell membranes, release of neurotransmitters and excitotoxicity, depletion of growth factors, and energy loss, all of which result in neuronal cell death. The therapeutic approach of preventing or diminishing the secondary degeneration that accompanies CNS trauma is termed neuroprotection. This approach seeks ways to endow the damaged CNS with means of coping with the stressful conditions, either by neutralizing the mediators of toxicity or by increasing the resistance of the tissue to the toxicity. Among the neuroprotective strategies devised to date are the use of antioxidants, free-radical scavengers, corticosteroids such as methylprednisolone, *N*-methyl-D-aspartate (NMDA) receptor antagonists, and the reduction of brain temperature (Schwartz et al., 1999c; Yoles and Schwartz, 1998).

Rats and mice injected with T cells specific to myelin-associated antigens showed better recovery from CNS injury than untreated animals, regardless of the virulence of the T cells used. After partial axonal injury of the rat optic nerve, the number of surviving axons with viable cell bodies (retinal ganglion cells) was significantly higher in rats treated on the day of the injury by systemic injection of T cells specific to MBP, or to an MBP-derived peptide, than in untreated rats. T cells specific to a peptide derived from heat-shock protein or to the nonself antigen ovalbumin had no such effect (Moalem et al., 1999b; Schwartz et al., 1999b). The observed effect was even more dramatic in the spinal cord, where anti-MBP T cells injected within a week after injury resulted in much better functional recovery (assessed in terms of locomotor activity) than in untreated rats. The observations were confirmed by morphological analyses, including magnetic resonance imaging (MRI) (Hauben et al., 2000a,b). These results led us to formulate a novel concept of protective autoimmunity (Moalem et al., 1999b; Schwartz et al., 1999b).

Neuroprotection by autoimmune T cells was not restricted to the use of encephalitogenic T cells, but could also be obtained with T cells directed to nonencephalitogenic epitopes (Moalem et al., 1999a,b). In addition to this passive immunization, effective neuroprotection was obtained by active immunization of rats with myelin-derived peptides (Hauben et al., 2000a; Fisher et al., 2000). The choice of both peptide and adjuvant was critical (Hauben et al., submitted). Our group recently demonstrated a neuroprotective effect in the rat optic nerve when the CNS self-antigen used for active immunization was replaced by a nonencephalitogenic synthetic antigen that cross-reacts with the CNS self-antigen. The synthetic antigen chosen for this experiment was Copolymer-1 (Cop-1), used clinically as a suppressor in the treatment of patients with multiple sclerosis, an autoimmune disease (Kipnis et al., 2000).

Taken together, these results strongly suggested that some forms of T cells which recognize myelin-associated self-antigens can exert a neuroprotective effect. Some important questions remain. For example, what is the nature of the mechanism underlying the neuroprotective effect? Is the observed neuroprotection a physiological response to injury, and is it restricted to insults sustained by axons?

5. Mechanisms underlying the neuroprotective effect of the autoimmune T cells

Analysis of the electrophysiological activity of the optic nerve at different times after injury and anti-MBP T cell injection showed that neuroprotection was preceded by a transient reduction in nerve conduction. There are several possible explanations for this. The observed neuroprotective effect might be caused, at least in part, by a T cell-induced transient reduction in the nerve's electrophysiological activity. Induction of a resting state in the damaged nerve was shown to transiently reduce the nerve's metabolic requirements and prevent energy depletion, thus helping to preserve neuronal viability in a manner similar to hypothermia-induced neuroprotection (Moalem et al., 1999b). It is also possible that the neuroprotective activity of the T cells is independent of their effect on the nerve's conductivity.

An alternative or additional mechanism might involve neurotrophins, shown in a number of studies to participate in the inflammatory response. Recently, nerve growth factor (NGF) was shown to be expressed in lymphocytes and macrophages (Ehrhard et al., 1993; Hikawa and Takenaka, 1996; Kerschensteiner et al., 1999; Lambiase et al., 1997; Santambrogio et al., 1994). Expression of

neurotrophin mRNA was detected in spleen, in thymus and in inflamed tissues.

T cells of different antigenic specificities were found by our group to express mRNA and protein specific to NGF, BDNF, NT-3, and NT-4/5. Secretion of these neurotrophins was significantly increased after reactivation of the T cells by their specific antigens (Moalem et al., 2000b). It thus appears that only CNS autoimmune T cells, upon recognizing their antigen, can secrete increased amounts of neurotrophins in injured optic nerves. This would explain why only T cells specific to myelin, or to antigens that cross-react with myelin, have neuroprotective properties. Support for the feasibility of a neurotrophic mechanism comes from the finding that mRNA for TrkA, TrkB, and p75 receptors is expressed in the injured optic nerve, pointing to an ability of T cell-derived neurotrophins to mediate their effects via these specific receptors (Moalem et al., 2000b). If indeed the neurotrophin theory is correct, why should therapy with neurotrophic factors derived from a T cell source be preferable to therapy with a single neurotrophic factor? This question will be discussed below.

6. Autoimmune neuroprotection is a beneficial spontaneous physiological response awakened by the injury

The results summarized in Section 4 showed that manipulation of the adaptive response directed to self can be beneficial in the context of CNS trauma. This raised a fundamental question: does the beneficial effect represent a physiological response, or is it merely the result of immunological intervention? Experiments in our laboratory showed that splenocytes from rats with a week-old spinal cord contusion exert neuroprotective activity when transferred to rats with a newly sustained CNS injury. No such neuroprotection was observed in adult rats that had been subjected to thymectomy at birth. These findings suggested that CNS injury in the rat awakens a beneficial systemic autoimmune neuroprotective response that is absent in thymectomized rats and can be transferred by splenocytes into naïve rats (Yoles et al., submitted). The magnitude of the response was dose-related, suggesting that the injury triggers T cell-mediated immune effects that have the potential both for neuroprotection and for neuronal destruction. It is possible that the same T cell is capable of both types of response, and that provided that the cell numbers are low enough, the beneficial activity outweighs the harmful effect. Alternatively, there might be two different populations of lymphocytes present in different numbers and having different potencies. In both cases, our results would imply that the two activities are regulated differently (Yoles et al., submitted).

Recent experiments in our laboratory showed that adult thymectomized rats cope less well with the stress induced by traumatic injury to the optic nerve or spinal cord than do control rats with an intact thymus, and thus their outcome after CNS insult is worse than that of normal rats (Yoles et al., 2000). These results further substantiate the notion that injury evokes a T cell-mediated beneficial response which reduces the spread of damage. Absence of this response, for example in thymectomized rats, significantly worsens the outcome of the injury.

7. Discussion

Studies in our laboratory showed that the spontaneous post-injury dialog between the CNS and macrophages and T cells differs from that in the PNS. T cell accumulation at a site of CNS injury was significantly augmented by systemic injection of activated T cell lines of various antigen specificities. Surprisingly, however, only autoimmune T cells against a CNS self component protected neurons from secondary degeneration after CNS injury. These findings suggested that the participation of activated autoimmune T cells, although normally restricted after CNS injury, might be essential for CNS protection. Our present theory is that immune privilege is an optimal solution for ongoing maintenance of the intact CNS, but may be disadvantageous for maintenance and repair of the injured CNS. It is possible that the acquisition of CNS immune privilege during evolution rendered the CNS capable of maintaining highly integrated neural functions under normal conditions, but with concomitant loss of its ability to regenerate and recover after injury.

The adaptive immune response has generally been considered as an immune activity evoked to enable the organism to cope with stressful conditions caused by pathogens. Thus, immunologists have viewed the functions of the adaptive immune response as neutralizing pathogens, preventing pathogen invasion of the tissue, or counteracting the damage caused by pathogens that manage to invade. The damage caused by trauma, however, does not involve pathogens, and was therefore not viewed by immunologists as posing the type of danger to the tissue that necessitates an adaptive immune response.

It was suggested many years ago (Burnet, 1971) that an adaptive immune response would be evoked unless the pathogen was recognized as self. Opinions differ as to the mechanisms by which self becomes invisible to the immune system (for example by clonal deletion, anergy, or tolerance) (Bretscher and Cohn, 1970; Cohen, 1988; Jameson et al., 1995; Janeway, 1992; Jerne, 1984). Some authors have proposed that autoimmunity, once established, might be harmless or even useful. In the 'danger signal' theory, which basically argues against discrimination between self and nonself in characterizing the signals triggering a beneficial immune response, the response to self is viewed as a by-product of a response to a pathogen, a side effect that soon decays in the absence of a second

signal to maintain it (Matzinger, 1994). On the basis of our results, we suggest that the anti-self immune activity evoked in response to trauma in the CNS is a purposeful physiological event. If trauma can indeed act as a stress signal that activates a helpful immune response, a number of questions arise: does this occur in all tissues? If not, why not? Does the trauma-related stress signal vary from tissue to tissue? Since the role of the immune system is tissue protection, defense and maintenance, does the signal always operate for the organism's benefit? How is it related to autoimmune disease?

It is possible that what determines whether or not a purposeful autoimmune response will be activated will depend on what poses the greater threat to the organism: the trauma-induced damage that leads to degeneration and tissue loss, or the risk of the negative side effect of the autoimmune response. Our finding that autoimmunity has a neuroprotective function after CNS trauma (Hauben et al., 2000a; Moalem et al., 1999a,b, 2000a,b) is particularly interesting in view of the well-known catastrophic consequences of trauma to the CNS as compared with other tissues, and hence the importance of arresting the progression of CNS damage. Because terminally damaged neurons are irreplaceable, loss of cells is more devastating in the CNS than in any other tissue. Accordingly, trauma in the CNS potentially poses more of a threat to the individual than trauma in any other tissue, and the distress signal elicited by trauma in the CNS can therefore be expected to be more profound. For example, the traumatized CNS might transmit — in addition to the signal sent by the damage itself — a second, as yet unidentified distress signal, thereby converting T cells into effector helper cells with trauma-related activity. This might imply that in traumatically injured non-CNS tissues that do not evoke an autoimmune response (beneficial or otherwise), the second signal may be insufficient to activate T cells and/or to maintain them in an active form that enables them to become effectors. The specificity of the evoked T cells (in terms of the self-epitopes that activate them and are recognized by them) might, even in the CNS, vary according to the site of the injury. It is conceivable that trauma-related distress signals activate T cells of other relevant self-epitopes for protective purposes.

Another aspect of the nature of the protective autoimmune response concerns the mediators enabling its expression in the context of pathogen-free damage. It is possible that the active molecules produced by the effector helper T cells after trauma-associated damage are neurotrophins, and that their secretion by the effector (autoimmune) T cells is antigen-dependent, similar to the documented secretion of cytokines by effector helper T cells after pathogen-induced damage. Alternatively, it is possible that helper T cells which engage in dialog with traumatized tissue in general, or with traumatized CNS tissue in particular, represent effector cells whose phenotype has yet to be identified.

Our results further suggest that nonpathogenic damage to CNS tissue triggers a signal to the immune system to assist in protecting the tissue against the spread of damage. The fact that the spontaneous T cell response does not exert enough protection to cause significant improvement after CNS injury might be attributable to the limited number of endogenous T cells, or an inappropriate phenotype of the T cells that accumulate at the injury site, or both. To better understand the role of T cells in neuroprotection, future studies will need to investigate the phenotype and the antigen specificity of the T cells isolated from the CNS injury site. This view of beneficial autoimmunity in the context of CNS trauma may provide an explanation for the high incidence of autoimmunity in healthy individuals, a phenomenon viewed by some scientists as an indication that autoimmunity may not always be harmful, and may even be useful.

Adoptive transfer of activated autoimmune T cells specific to a CNS antigen is a potential cell therapy that offers some advantages. Firstly, only a single systemic injection is needed, thus avoiding the danger of invasive entry into the CNS. Secondly, the activated T cells cross the blood–brain barrier and accumulate specifically at CNS lesions. Thirdly, since T cell accumulation at a site of CNS injury was observed from day 3 to day 21 after injury (Moalem et al., 1999a,b), these T cells would presumably be capable of continuous release of neurotrophins at the CNS injury site during that period. The timing and dynamics of such neurotrophin release might be in accordance with the needs of the tissue. T cells in the injured CNS are eliminated by self-limiting mechanisms involving apoptosis, allowing the response to be extinguished. Fourthly, the benefit provided by the autoimmune anti-MBP T cells could be mediated by several mechanisms working in concert. The inflammatory process and antigen presentation at the site of injury could activate CNS-specific T cells to secrete molecules that induce a resting state in the injured nerve, while sustaining the nerve with neurotrophins.

This new view, once fully understood, is likely to open up a novel approach to the treatment of chronic and acute injuries by exploiting the adaptive arm of the immune system in the interest of recovery from trauma. This resource, up to now neglected and even shunned by immunologists, might represent a therapeutic gold mine. Its exploration can also be expected to unravel some long-standing enigmas, including the meaning of a danger signal in immunology, and the way in which the immune response is evoked.

The use of safe synthetic peptides that resemble and cross-activate myelin-associated self peptides may constitute a strategy for developing anti-self immunity for neuroprotection. Future studies should seek to identify the specific antigen(s) active in any particular disease, the optimal timing and type of immunization (passive or active), and the most appropriate adjuvant, in order to best

exploit the long-neglected immune system for the development of a physiological approach to therapy enabling maximal benefit with minimal risk.

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